(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 September 2001 (20.09.2001)

PCT

(10) International Publication Number
WO 01/68649 A1

(51) International Patent Classification[7]: C07D 471/04, 401/10

(21) International Application Number: PCT/KR01/00399

(22) International Filing Date: 14 March 2001 (14.03.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2000/13011 15 March 2000 (15.03.2000) KR

(71) Applicants *(for all designated States except US)*: **LG CHEM INVESTMENT LTD.** [KR/KR]; 20, Yoido-dong, Yongdungpo-ku, Seoul 150-010 (KR). **KIM, Yeong, Dae** [KR/KR]; Hanbit Apt. #108-1104, 99, Uheun-dong, Yusong-gu, Taejon 305-333 (KR). **CHOI, Hoon** [KR/KR]; 339-17, Junmin-dong, Yusong-gu, Taejon 305-390 (KR). **KIM, Won, Sup** [KR/KR]; LG Hana Apt. #103-106, Shinsung-dong, Yusong-gu, Taejon 305-345 (KR).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **KIM, Bong, Chan** [KR/KR]; LG Apt. #3-402, 386-1, Doryong-dong, Yusong-gu, Taejon 305-340 (KR).

(74) Agent: **CHOI, Kyu-Pal**; 824-11, Yeoksam-dong, Kangnam-ku, Seoul 135-080 (KR).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/68649 A1

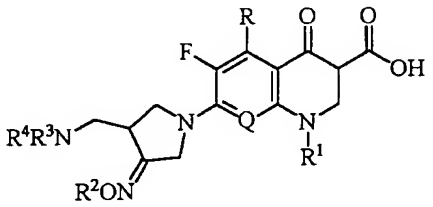
(54) Title: NOVEL PROCESS FOR THE PREPARATION OF A QUINOLINE CARBOXYLIC ACID DERIVATIVE HAVING A 7-(4-AMINOMETHYL-3-OXIME)PYRROLIDINE SUBSTITUENT

(57) Abstract: The present invention relates to a novel process for preparing quinoline carboxylic acid antimicrobials having a 7-(4-aminomethyl-3-oxime)pyrrolidine substituent, e.g. gemifloxacin, or salt thereof, wherein a specific surfactant is used so that the filtration time can be significantly reduced compared with the prior art method.

NOVEL PROCESS FOR THE PREPARATION OF A QUINOLINE CARBOXYLIC ACID DERIVATIVE HAVING A 7-(4-AMINOMETHYL-3-OXIME)PYRROLIDINE SUBSTITUENT

TECHNICAL FIELD

The present invention relates to a novel process for preparing quinoline carboxylic acid derivatives having a 7-(4-aminomethyl-3-oxime)pyrrolidine substituent represented by the following formula (3):



(3)

in which

Q represents C-H, C-F, C-Cl, C-OH, C-O-methyl, or N,

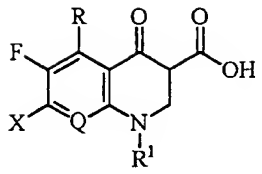
R represents hydrogen, methyl, or amino,

R^1 represents cyclopropyl, ethyl or phenyl which is substituted by one or more fluorine atoms,

R^2 represents hydrogen, straight-chain or branched alkyl having 1 to 4 carbon atoms, aryl or allyl, and

R^3 and R^4 independently of one another represent hydrogen or C_1-C_3-alkyl, or together with the nitrogen atom to which they are attached may form a cycle, or a salt thereof

which comprises coupling a compound represented by the following formula (1):

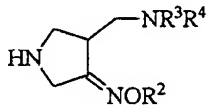


(1) .

in which

Q, R and R^1 are as defined for formula (3), and

X represents a leaving group, preferably halogen, or a salt thereof, with a compound represented by the following formula (2):



(2) .

in which

R^2, R^3 and R^4 are as defined for formula (3), or a salt thereof.

BACKGROUND ART

The compounds of formula (3), which are disclosed in Korean Patent Application 94-13604, are quinolone antimicrobials. A particular compound of formula (3) which may be mentioned is (R,S)-7-(3-aminomethyl-4-*syn*-methoxyimino-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (gemifloxacin) and pharmaceutically acceptable salts thereof. Korean Patent Application No 98-80504 discloses a preferred form of this compound namely (R,S)-7-(3-aminomethyl-4-*syn*-methoxyimino-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic methanesulfonate and hydrates thereof, in particular the sesquihydrate.

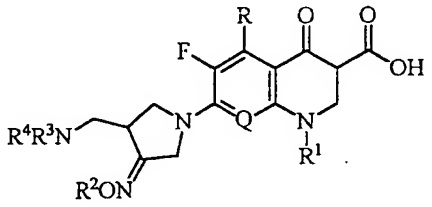
The free base of formula (3) can therefore be considered as a key intermediate for the preparation of the salts of formula (3) and will exert a direct influence on the quality of the final product. Attempts have been made to prepare the compounds of formula (3)

with an improved purity using water as the solvent instead of a solvent mixture of acetonitrile/water (see PCT/GB00/03366). However, the conventionally used solvents including water have the problem that the time required for filtration is longer than is desirable for use on a commercial scale where short cycle times are advantageous.

DISCLOSURE OF INVENTION

Thus, the present inventors have conducted extensive studies to solve this problem in preparing a quinoline carboxylic acid derivative having a 7-(4-aminomethyl-3-oxime)pyrrolidine substituent and salts thereof. As a result, we have found that by employing a new process where a surfactant is introduced into the reaction solution, the filtration time may be significantly reduced without any influence on the reactivity. The present invention is based on this finding.

Therefore, the object of the present invention is to provide a process for preparing a quinoline carboxylic acid derivative having a 7-(4-aminomethyl-3-oxime)pyrrolidine substituent represented by the following formula (3):



(3) .

in which

Q represents C-H, C-F, C-Cl, C-OH, C-O-methyl, or N,

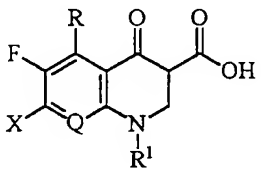
R represents hydrogen, methyl, or amino,

R^1 represents cyclopropyl, ethyl or phenyl which is substituted by one or more fluorine atoms,

R^2 represents hydrogen, straight-chain or branched alkyl having 1 to 4 carbon atoms, aryl

or allyl, and

R^3 and R^4 independently of one another represent hydrogen or C_1-C_3-alkyl, or together with the nitrogen atom to which they are attached may form a cycle, or a salt thereof which comprises coupling a compound represented by the following formula (1):



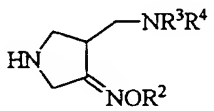
(1)

in which

Q, R and R^1 are as defined for formula (3), and

X represents a leaving group, preferably halogen, or a salt thereof,

with a compound represented by the following formula (2):



(2)

in which

R^2, R^3 and R^4 are as defined for formula (3), or a salt thereof,

in a solvent in the presence of a base and a surfactant, and then filtering the resulting compound of formula (3);

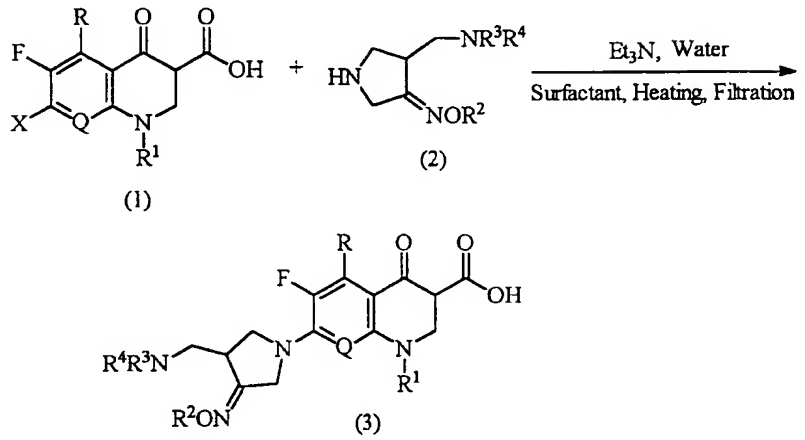
and optionally forming a pharmaceutically acceptable salt and/or hydrate thereof.

BEST MODE FOR CARRYING OUT THE INVENTION

According to the prior art method a compound of formula (3) is typically prepared by introducing the compound of formula (1) into a solvent, e.g. water, adding dropwise a base, e.g. triethylamine, to make a thoroughly clear solution, adding the compound of formula (2) into the reaction solution, and filtering the reaction solution after the completion of reaction.

However, according to the present invention, the compound of formula (3) is prepared as depicted in the following Reaction Scheme (1):

Reaction Scheme (1)



Using the process of the present invention, the filtration time is reduced by 5 to 20 times, preferably 15 to 20 times, that obtained using the prior art method. The reaction time may also be reduced to 2~3 hours from 8~10 hours by raising the reaction temperature. Thereby, the cycle time, which is a very important economical factor in a commercial process, can be significantly reduced.

The pharmaceutically acceptable salts of the compounds of formula (3) include those with acids generally known and used in the technical field to which quinolone derivatives or pyrrolidine derivatives pertain. Salts with methanesulfonic acid may be specifically mentioned, methanesulfonates and hydrates thereof may be synthesised from the free base as described in Korean Patent Application No 98-80504.

Salts of the compounds of formulae (1) and (2) which may be used in the process of the invention include salts known to those skilled in the art. Particular salts of the compounds of formula (2) which may be mentioned include the hydrochloride,

trifluoroacetate and sulfate salts as described in PCT/KR99/00099, and in particular the methanesulfonates as described in PCT/GB00/03358.

The surfactant, base, solvent, etc. used in the process of the present invention can be appropriately selected from those that do not adversely affect the reaction. The preferred reaction conditions including the amount and kind of the surfactant, base and solvent, reaction temperature, reaction order, etc. are as follows:

The preferred surfactant for use in the present invention is metolose which is a cellulose ether, i.e., methyl cellulose or hydroxypropyl methyl cellulose, more specifically, methyl cellulose, SM-25 (Shinetsu) or hydroxypropyl methyl cellulose 2910, 60SH-50 (Shinetsu) can be mentioned. For optimal filtration, generally, the amount of surfactant ranges between 0.5 and 3.0% by weight with respect to the compound of formula (1).

As the base, an organic base such as triethylamine, pyridine, etc., preferably triethylamine, is used, preferably in an amount of 2 to 5 equivalents with respect to the compound of formula (1).

As the solvent, one or more selected from the group consisting of acetonitrile, water, alcohols, dimethylformamide and dimethylsulfoxide can be preferably used, but water is particularly preferable in view of the purity of the resulting product.

The preferred reaction temperature is between about 0 and 40℃, and the surfactant will be selected according to the reaction temperature to obtain optimal results. For example, in the case of room temperature reaction, the best result is obtained using methyl cellulose, SM-25 (reduction by about 10 times in the filtration time) and in the case of reaction at 40℃, the best result is obtained using hydroxypropyl methyl cellulose 2910, 60SH-50 (reduction by about 15 to 20 times in the filtration time).

Under the conditions mentioned above, the process of the present invention may

be carried out according to one of the following procedures:

a) the compound of formula (1) or salt thereof is introduced into a solvent, a base is added (ideally to make a thoroughly clear solution), a surfactant is added, the reaction temperature is optionally raised, the compound of formula (2) or salt thereof is added, and then the reaction solution is filtered after the reaction is completed; or

b) the compound of formula (1) or salt thereof and a surfactant are introduced into a solvent, a base is added (preferably dropwise, if desired, the base may be slowly added over about 2 hours), the reaction temperature is optionally raised, the compound of formula (2) or salt thereof is added, and then the reaction solution is filtered after the reaction is completed and, optionally after the reaction solution is allowed to stand for 2 to 3 hours at room temperature.

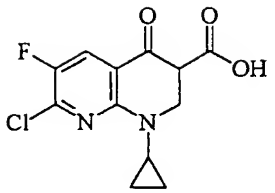
All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The present invention will be more specifically explained by the following examples. However, it should be understood that those examples are intended to illustrate the present invention but not in any manner to limit the scope of the present invention.

Comparative Example 1

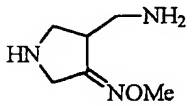
Preparation of 7-(4-aminomethyl-3-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro[1,8]naphthyridine-3-carboxylic acid according to the prior art method

A compound of the following formula (1a) (30.0g, 106.14mmol):



(1a) .

and water(300 ㎖, 10 ㎖/g) were introduced into a 500 ㎖ reactor and the mixture was stirred at room temperature(24～26℃). 3.4 Equivalents of triethylamine(36.51g, 360.81 mmol) was added thereto at room temperature, with the temperature being raised to about 30℃, stirred for 10 minutes for making a clear solution, and then the temperature was cooled to 16～20℃. A compound of the following formula (2a) (37.46g, 111.68mmol):



(2a)

2MSA

was added at 16～20℃ and stirred at room temperature. After stirring for 15.5 hours, the reaction was completed (HPLC analysis that the content of the compound of formula (1a) in the reaction solution is decreased to 2% or less, is regarded to show the completion of reaction). After the reaction was completed, the mixture was filtered through a glass filter, consecutively washed with water(150 ㎖) and ethanol(150 ㎖), and then dried under nitrogen gas stream to give the title compound (37.32g; Content of residual solvent 10.7%; Yield 81%) as a solid. The first filtration time was 52 minutes, the second 43 minutes, and the third 42 minutes, respectively.

Example 1

Preparation of 7-(4-aminomethyl-3-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro[1,8]naphthyridine-3-carboxylic acid wherein surfactant is added after base and the reaction is carried out at room temperature

The compound of formula (1a) (30.0g, 106.14mmol) used in Comparative Example 1 and water (300 ㎖, 10 ㎖/g) were introduced into a 500 ㎖ reactor, and the resulting mixture was stirred at room temperature(24～26℃). 3.4 Equivalents of triethylamine (36.51g, 360.81 mmol) was added thereto at room temperature, with the

temperature being raised to about 30℃, and stirred for 10 minutes for making a clear solution. 300mg (1.0wt%/Compound(1a)) of methyl cellulose, SM-25, a surfactant, was added and stirred for 10minutes. Then, the compound of formula (2a) (37.46g, 111.68mmol) used in Comparative Example 1 was added thereto at room temperature and stirred. After stirring for 16.5 hours, the reaction was completed (HPLC analysis that the content of the compound of formula (1a) in the reaction solution is decreased to 2% or less, is regarded to show the completion of reaction). The mixture after completion of reaction was filtered through a glass filter, consecutively washed with water(150 ㎖) and ethanol(150 ㎖), and then dried under nitrogen gas stream to give the title compound (34.31g; content of residual solvent 6.5%; Yield 78%) as a solid. The first filtration time was 5 minutes, the second 5 minutes, and the third 5 minutes, respectively, the total time of which was about 9 times shorter than that of Comparative Example 1.

Example 2

Preparation of 7-(4-aminomethyl-3-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro[1,8]naphthyridine-3-carboxylic acid wherein surfactant is added before base and the reaction is carried out at room temperature

The compound of formula (1a) (30.0g, 106.14mmol) used in Comparative Example 1, 300mg (1.0wt.%/Compound(1a)) of hydroxypropyl methyl cellulose 2910, 60SH-50 as a surfactant, and water(300 ㎖, 10 ㎖/g) were introduced into a 500 ㎖ reactor, and the resulting mixture was stirred at room temperature(24～26℃). 3.4 Equivalents of triethylamine (36.51g, 360.81mmol) was added thereto at room temperature, with the temperature being raised to about 30℃, and stirred for 10 minutes for making a clear solution. The compound of formula (2a) (37.46g, 111.68mmol) used in Comparative Example 1 was added thereto at room temperature and stirred. Thereafter, the same procedure as Example 1 was carried out except that the reaction time was 15 hours to give the title compound (32.25g; content of residual solvent 7.49%; Yield 72%) as a solid. The first filtration time was 6 minutes, the second 5 minutes, and the third 6 minutes, respectively, the total time of which was about 8 times shorter than that of Comparative

Example 1.

Example 3

Preparation of 7-(4-aminomethyl-3-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro[1,8]naphthyridine-3-carboxylic acid wherein surfactant is added before base and the reaction is carried out at 40℃

The compound of formula (1a) (30.0g, 106.14mmol) used in Comparative Example 1, 300mg (1.0wt.%/Compound(1a)) of hydroxypropyl methyl cellulose 2910, 60SH-50 as a surfactant, and water(300 mℓ, 10 mℓ/g) were introduced into a 500 mℓ reactor, and the resulting mixture was stirred at room temperature(24～26℃). 3.4 Equivalents of triethylamine (36.51g, 360.81mmol) was added thereto at room temperature, with the temperature being raised to about 30℃, and stirred for 10 minutes for making a clear solution. After the temperature of this reaction solution was raised to 40℃, the compound of formula (2a) (37.46g, 111.68mmol) used in Comparative Example 1 was added thereto at the same temperature, stirred, and reacted for 3.5 hours. The reaction solution was cooled to room temperature over 40 minutes and then filtered, washed and dried according to the same procedure as Example 1 to give the title compound (34.16g; content of residual solvent 7.4%; Yield 77%) as a solid. The first filtration time was 3 minutes, the second 2 minutes, and the third 3 minutes, respectively, the total time of which was about 17 times shorter than that of Comparative Example 1.

Example 4

Preparation of 7-(4-aminomethyl-3-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro[1,8]naphthyridine-3-carboxylic acid wherein base is added as slowly as possible and the reaction is carried out at 40℃

The same procedure as Example 3 was carried out except that the base triethylamine is slowly added over 2 hours and the reaction time was 2.5 hours to give the title compound (34.52g; content of residual solvent 6.4%; Yield 78%) as a solid. The first

filtration time was 3 minutes, the second 3 minutes, and the third 3 minutes, respectively, the total time of which was about 15 times shorter than that of Comparative Example 1.

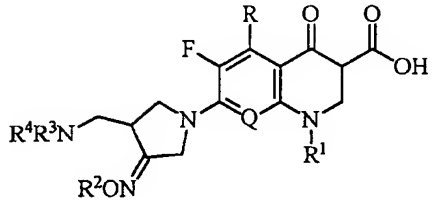
Example 5

Preparation of 7-(4-aminomethyl-3-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro[1,8]naphthyridine-3-carboxylic acid wherein surfactant is added before base, the reaction solution is allowed to stand for 2~3 hours after reaction completion at room temperature, and the reaction is carried out at 40℃

The same procedure as Example 3 was carried out except that the reaction time was 2.5 hours and the reaction solution was allowed to stand for 2~3 hours after reaction completion to give the title compound (33.23g; content of residual solvent 6.5%; Yield 75%) as a solid. The first filtration time was 3 minutes, the second 2 minutes, and the third 2 minutes, respectively, the total time of which was about 20 times shorter than that of Comparative Example 1.

CLAIMS

1. A process for preparing a compound represented by the following formula (3):



(3) .

in which

Q represents C-H, C-F, C-Cl, C-OH, C-O-methyl, or N,

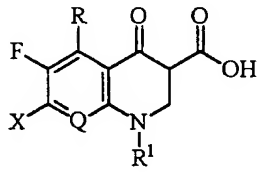
R represents hydrogen, methyl, or amino,

R^1 represents cyclopropyl, ethyl or phenyl which is substituted by one or more fluorine atoms,

R^2 represents hydrogen, straight-chain or branched alkyl having 1 to 4 carbon atoms, aryl or allyl, and

R^3 and R^4 independently of one another represent hydrogen or C_1-C_3-alkyl, or together with the nitrogen atom to which they are attached may form a cycle, or a salt thereof

which comprises coupling a compound represented by the following formula (1):



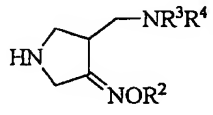
(1) .

in which

Q, R and R^1 are as defined for formula (3), and

X represents a leaving group, preferably halogen, or a salt thereof,

with a compound represented by the following formula (2):



(2) .

in which

R^2, R^3 and R^4 are as defined for formula (3), or a salt thereof,

in a solvent in the presence of a base and a surfactant, and then filtering the resulting compound of formula (3);

and optionally forming a pharmaceutically acceptable salt and/or hydrate thereof.

2. The process of claim 1 wherein the compound of formula (1), or a salt thereof, is introduced into a solvent to which a base, a surfactant and the compound of formula (2) or a salt thereof are added consecutively, and then the reaction solution is filtered.

3. The process of claim 1 wherein the compound of formula (1), or a salt thereof, and a surfactant are introduced into a solvent to which a base and the compound of formula (2) or a salt thereof are added consecutively, and then the reaction solution is filtered.

4. The process of claim 3 wherein the base is added dropwise.

5. The process of claim 3 wherein the reaction temperature is 40℃ and the reaction solution is allowed to stand for 2 to 3 hours at room temperature before filtration.

6. The process of any one of the preceding claims wherein the surfactant is a cellulose ether.

7. The process of claim 6 wherein the cellulose ether is hydroxypropyl methyl cellulose or methyl cellulose.

8. The process of any one of the preceding claims wherein the surfactant is used in an amount of 0.5 to 3.0% by weight with respect to the compound of formula (1).

9. The process of any one of the preceding claims wherein the reaction temperature is between 0 and 40℃.

10. The process of any one of the preceding claims wherein the base is triethylamine and the solvent is water.

11. The process of any one of the preceding claims wherein the compound of formula (3) is (R,S)-7-(3-aminomethyl-4-*syn*-methoxyimino-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid or a pharmaceutically acceptable salt thereof.

12. The process of claim 11 wherein the compound of formula (3) is (R,S)-7-(3-aminomethyl-4-*syn*-methoxyimino-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic methanesulfonate or a hydrate thereof.

13. The process of claim 12 wherein the compound of formula (3) is (R,S)-7-(3-aminomethyl-4-*syn*-methoxyimino-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic methanesulfonate sesquihydrate.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR01/00399

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 C07D 471/04, C07D 401/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimun documentation searched (classification system followed by classification symbols)

IPC7 C07D

Documentation searched other than minimun documentation to the extent that such documents are included in the fileds searched

KR JP IPC as above

Electronic data base consulted during the international search (name of data base and, where practicable, search trerms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 688 772 A (LG Chemical Limited) 27 December 1995 cited in the application, see the whole document	1-13
A	WO 98 42705 A (LG Chemical Limited) 1 October 1998 cited in the application, see the whole document	11-13
A	KR 222081 B (LG Chemical Limited) 1 October 1999 see the whole document	11-13
A	WO 00 17199 A (SMITHKLINE BEECHAM P.L.C.) 30 March 2000 see the whole document	11-13

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevence

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevence; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevence; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 JULY 2001 (25.07.2001)	27 JULY 2001 (27.07.2001)

Name and mailing address of the ISA/KR

Korean Intellectual Property Office
Government Complex-Daejeon, Dunsan-dong, Seo-gu, Daejeon Metropolitan City 302-701, Republic of Korea

Facsimile No. 82-42-472-7140

Authorized officer

KANG, Choon Won

Telephone No. 82-42-481-5608

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR01/00399

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0688772 A	27-12-95	US 5962468 A	05-10-99
		US 5869670 A	09-02-99
		US 5840916 A	24-11-98
		US 5776944 A	07-07-98
		US 5698570 A	16-12-97
		US 5633262 A	27-05-97
		RU 2120940 C	27-10-98
		KR 222083 B	01-10-99
		KR 222082 B	01-10-99
		KR 131999 B	17-04-98
		JP 8041050 A	13-02-96
		JP 2742248 B	22-04-98
		EP 668772 B	06-05-99
		DK 668772 T	01-11-99
		DE 69509442 T	02-09-99
		DE 69509442 C	10-06-99
		CN 1114959 A	17-01-96
		CN 1058010 B	01-11-00
		CA 2151890 C	12-01-99
		CA 2151890 AA	17-12-95
		BR 1101096 A	18-04-00
WO 9842705 A	01-10-98	TR 9902313 T	21-12-99
		SK 123699 A	14-08-00
		PL 335812 A	22-05-00
		NO 994595 A	21-09-99
		JP 510484 T	15-08-00
		HU 00728 AB	28-09-00
		EP 981527 A	01-03-00
		CN 1251101 T	19-04-00
		BR 9808290 A	16-05-00
		BG 103750 A	30-06-00
		AU 6636698 A	20-10-98
		AU 726634 B	16-11-00
		AP 9901649 A	30-09-99
KR 222081 B	01-10-99	NONE	
WO 0017199 A	30-03-00	NO 20011290 A	14-03-01
		EP 1114050 A	11-07-01
		BR 9913858 A	12-06-01
		AU 6328399 A	10-04-00

This Page is Inserted by IFW Indexing and Scanning Operations and is not part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☑ FADED TEXT OR DRAWING
- ☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.
As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.